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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,900	02/24/2004	Eugene R. Cooper	029318-1003	1015

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EXAMINER	
TRAN, SUSAN T	
ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,900	COOPER ET AL.	
	Examiner	Art Unit	
	S. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 9, 10, 12, 14-17, 26-29, 32-35, 38, 39, 41, 50, 52-55, 58, 59, 61 and 63-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Turck et al. US 6,184,220.

Turck teaches an oral suspension comprising one or more active substances of the NSAID type, particularly the antirheumatic agent, meloxicam (abstract; and column 4, lines 66 through column 5, lines 1-67). Meloxicam has particle size such that at least 90% of the particles are smaller than 10 μm (column 4, lines 35-46). Turck further teaches meloxicam is stabilized by the addition of silicon dioxide and hydrophilic polymer (abstract; and column 4, lines 13-45). The suspension further comprises other additives such as flavoring agent, sweetening agent, and excipients (column 6, lines 62 through column 7, lines 1-23). Turck also teaches a process for preparing the stabilized drug particle comprising grinding the drug, and then mixing the drug with silicon dioxide using homogenizing process (column 7, lines 35-59; example 1; and column 10, lines 15-54). Turck further teaches the suspension has a T_{max} of 1.5-5 hours (column 10, lines 1-2).

It is noted that Turck does not explicitly teach the claimed properties such as claims 15 and 17. However, such limitations are inherent because Turck teaches the use of the same active agent having particle size that falls within the claimed range that result in the claim T_{max}, namely, meloxicam with at least 90% of the particles are smaller than 10 μm which has the T_{max} of 1.5 hours.

Claim Rejections - 35 USC § 103

Claims 1-17, 26-42 and 50-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turck et al., in view of Liversidge et al. WO 93/25190.

Turck is relied upon for the reason stated above, Turck does not teach the claimed surface stabilizer.

Liversidge teaches a dispersible nanoparticle having an effective average particle size of less than about 400 nm, the nanoparticle comprising NSAID and surface modifier (abstract; and page 2, lines 21-25). NSAID is present in crystalline phase, and in an amount 0.1%-60% (page 3, lines 31-35; and page 7, lines 31-33). Liversidge further teaches a pharmaceutical formulation for the treatment of a mammal, the formulation comprising the dispersible nanoparticle, and an acceptable carrier (page 2, lines 26-28). Liversidge also teaches a process for preparing the nanoparticle comprising the steps of dispersing an NSAID in a liquid dispersion medium; wet grinding the NSAID in the presence of grinding media, wherein the pH of said medium is within the range of 2-6; and adding surface modifier in an amount of 0.1-90% (page 7, lines 20 through column 8, lines 1-17; and pages 9-10). The claimed surface modifier is

disclosed in pages 5-6. Two or more surface modifiers can be used in combination (ID). The pharmaceutical formulation can be processed into dosage form such as solid, liquid for administration by parenteral, oral, rectal, and the like (page 11, lines 29-36). Thus, it would have been obvious to one of ordinary skill in the art to modify the process for preparing the active particle of Turck to include other surface stabilizer in view of the teachings of Liversidge to obtain the claimed invention. This is because Liversidge teaches that surface modified NSAID nanoparticles demonstrate reduced gastric irritation and a more rapid onset of action following administration (pages 2-3), because Turck teaches the use of surface stabilizing agents for stabilization purpose and to prevent agglomeration of the particles (column 3, lines 53-65), because Turck teaches the desirability for preparing a dosage form suitable for long term administration of meloxicam with reduced gastrointestinal side effects, and because Turck teaches the desirability to achieve rapid onset of meloxicam to ensure fastest possible dissolution of the active substance in the GI tract (column 1, lines 40-67; and column 4, lines 30-35).

Claims 18-25, 43-49 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turck et al., in view of Desai et al. WO 01/45706 A1 or Courteille et al. US 5,384,124.

Turck is relied upon for the reasons stated above. The cited references do not teach the second particle population.

Desai teaches a dual-release composition of low water soluble drug (COX-2 inhibitor) comprising first fraction of the drug in nano-particulate form having average

diameter of about 200 to about 400 nm and a D90 particle size less then about 5 μm (page 18); and a second fraction of the drug in micro-particulate form having D_{10} particle size of between 25 to about 100 μm (page 20, 1st paragraph). The first fraction nano-particle drug can be present alone or in combination with one or more excipient, such as nano-particles of the drug have a surface modifying agent (PEG-400) adsorbed on the surface thereof (page 18, 3rd through page 19). The weight ratio of the first to the second fraction of the drug in the composition is about 1:10 to about 10:1 (page 22, 3rd paragraph). The composition can be in an oral dosage form including tablet, pills, hard or soft capsule, lozenges, cachets, dispensable powder, granule, suspension or elixir (pages 37-38).

Courteille teaches a solid unitary composition comprising combination of nano-particle having diameter of less than 1 μm and micro-particle having diameter of between 1 μm to 2 mm (see abstract, column 2, lines 32-46). The mixture of nano/micro-particle contains one or more active agents of the same or different type (column 1, lines 66-68, and column 2, lines 23-31). The active agent can be selected from antibiotic, analgesic, tranquilizer, vitamins, and therapeutic agents for diseases of allergies, hormones, or gastrointestinal tract (column 5, lines 46-66). The mixture of nano/micro-particle is prepared by any known method (air-fluidized bed coating, turbine coating, simple extrusion, or micro-encapsulation) employing the use of a polymer or a macromolecular substance (surface stabilizer) selected from the group of cellulose derivatives, starch, polyamide, collagen, dextrin, gelatin, polyvinyl chloride or the like (column 2, lines 46-55, and column 3, lines 18-40). The mixture further comprises

stabilizing agent, surfactant, and biding agent (column 4, lines 20 through column 5, lines 1-28). Courteille further teaches the solid dosage form comprises immediate release with a secondary controlled release of mixture of nano/micro-particle (column 6, lines 16-50). The solid dosage form is to be incorporated into pharmaceutical oral dosage form (column 6, lines 51-56).

Thus, it would have been obvious to one of ordinary skill in the art to modify the composition of Turck to include the second particle population in view of the teachings of Desai or Courteille, because Desai and Courteille teaches compositions suitable for analgesic drugs including COX inhibitor, and because Turck teaches the desirability of obtaining a composition suitable for the treatment of conditions using NSAID active agents.

Response to Arguments

Applicant's arguments filed 07/02/08 have been fully considered but they are not persuasive.

Applicant argues that Turck fails to teach a surface stabilizer adsorbed on the surface of the meloxicam particles. Claim 1 requires at least one surface stabilizer adsorbed on the surface of the meloxicam particles. The Examiner explicitly acknowledges that, with respect to Claim 1, Turck does not teach a surface stabilizer: "Turck does not teach the claimed surface stabilizer" (Office Action, page 3, last full paragraph). For this reason alone, withdrawal of the anticipation rejection is warranted.

However, in response to applicant's argument that Turck dose not teach the surface stabilizer adsorbed on the surface of the meloxicam, it is noted that such property is inherent because Turck teaches the same process requires by the present invention. See for example claim 26 of the present invention, which recites "[a] method of making a nanoparticulate composition comprising contacting meloxicam particles with at least one surface stabilizer". Turck teaches contacting meloxicam with silicon dioxide and homogenizing the premixed in a suitable container (column 10, lines 39-43).

Applicant argues that Turck discloses that "at least 90% of the particles are smaller than 50 µm, preferably at least 50% of the particles are smaller than 10 µm, and most preferably about 90% of the particles are smaller than 10 µm" (column 4, lines 38-41). Claim 1 requires an effective average particle size of less than about 2000 nm. A D_{50} of 10 µm does not anticipate a D_{50} (the claimed "effective average") of less than 2000 nm, i.e. 2 µm. Likewise, a characterization of a distribution's D_{90} does not provide information to one of ordinary skill in the art about the D_{50} of that same distribution. For this additional reason, withdrawal of the anticipation rejection is warranted.

However, in response to applicant's argument, it is noted that Turck teaches through the patent that at least 50% (D_{50}) of the particles are smaller than 10 µm, not of 10 µm. Accordingly, smaller than 10 µm includes 2 µm or 2000 nm.

Applicant argues that claim 1 requires a composition in "comparative pharmacokinetic testing with a non-nanoparticulate formulation [sic] to exhibit a shorter

time to T_{max} when compared to the time to T_{max} of the non-nanoparticulate meloxicam formulation." Turck discloses that "the time for maximum plasma concentration on a single dose of meloxicam is T_{max}=2 h (1.5-5 h; suspension)" (column 9, line 67, through column 10, line 2). The Examiner contends that Turck's composition would have the same T_{max} as Applicant's claimed composition because Turck teaches meloxicam having the same particle size as the Applicant's invention (see Office Action, page 3, first full paragraph). The contention is incorrect, and proven so by the McGurk Declaration submitted on April 3, 2008. If Turck's composition had the same particle size, Turck's suspension should have the same time to T_{max} as reported in the McGurk Declaration. Such is not the case. In fact, the Applicant's nanoparticulate meloxicam was reported to have a mean T_{max} of 0.667 hours (see paragraph 8, Table 2), which is much shorter the mean T_{max} (2 h) (and even the raw data, 1.5-5 h) of Turck's suspension. Turck therefore does not teach the claimed limitation that the composition "in comparative pharmacokinetic testing with a non-nanoparticulate formulation of meloxicam having the same dosage strength and form, the composition exhibits a shorter time to T_{max} when compared to the time to T_{max} of the non-nanoparticulate meloxicam formulation." For this additional reason, the rejection cannot be maintained.

However, in response to applicant's argument that *if Turck's composition had the same particle size, Turck's suspension should have the same time to T_{max} as reported in the McGurk Declaration*, it is noted that the actual T_{max} is not claimed. The present claim 1 requires a comparative T_{max} of a nanoparticulate meloxicam to a non-nanoparticulate meloxicam, in which a nanoparticulate formulation exhibits a shorter

time to T_{max} when compared to the time to T_{max} of the non-nanoparticulate meloxicam formulation. According to the McGurk Declaration, non-nanoparticulate formulations exhibit a time to T_{max} of 3.500 and 4.750 (paragraph 8, Table 2). As admitted by applicant, Turck discloses that "the time for maximum plasma concentration on a single dose of meloxicam is T_{max}=2 h (1.5-5 h; suspension)". Therefore, Turck teaches a nanoparticulate meloxicam formulation that exhibits a shorter time to T_{max} when compared to the time to T_{max} of the non-nanoparticulate meloxicam formulation. Accordingly, the 102(b) rejection by Turck is maintained.

Applicant argues that Turck teaches that the SiO_2 forms a three-dimensional matrix of solid SiO_2 strands. Nothing in Liversidge teaches or suggests that its surface stabilizers are capable of forming such a structure. Despite the rejection citing to a general desirability of a less harmful (reduce gastric irritation) more stable (prevent agglomeration) composition, which applies to any pharmaceutical composition, the rejection fails to provide a specific reason why one of ordinary skill in the art would predictably expect that the surface stabilizers of Liversidge would perform the same as the three-dimensional, solid matrix forming strands of SiO_2. Accordingly, absent vague generalizations, the rejection lacks a rationale for one of ordinary skill in the art to make the simple substitution of one element for another. For at least these reasons, no *prima facie* case for obviousness has been made. In view of the foregoing, the rejection should be withdrawn.

In response to applicant's argument, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the present case, Liversidge teaches the use of surface modifier to maintain an average particle size of less than about 400 nm (page 2, lines 24-25). Turck teaches the desirability for obtaining particle of active agent of less than 10 μm. Thus, one of ordinary skill in the art would have been motivated to modify the surface of the active agent to maintain the particle size less than 10 μm in view of the teachings of Liversidge. Further, Liversidge teaches the desirability for preparing surface modified NSAID particles such as oxicams, *e.g.*, piroxicam. Turck teaches oxicams include piroxicam and meloxicam. Thus, one of ordinary skill in the art would have been motivated to optimize the surface modified particles of NSAID of Liversidge to include meloxicam.

Accordingly, the 103(a) rejection over Turck and Liversidge is maintained.

Applicant argues that the Examiner cited Desai and Courteille for their alleged teachings of the second particle population. Nevertheless, Desai and Courteille do not compensate for the deficiencies of Turck as discussed above. Therefore, withdrawal of the rejection is respectfully requested.

In response to applicant's argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the

primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1618